

**ADVANCING NEURAL TUBE DEFECT PREVENTION IN LOW-
AND MIDDLE-INCOME COUNTRIES THROUGH IMPROVED
FOLATE STATUS IN WOMEN OF REPRODUCTIVE AGE—**

*Proceedings From The Technical Consultation:
Folate Status In Women And Neural Tube Defect Prevention*



JULY 2017

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Foreword

Many countries have made great progress in reducing under-five mortality from infectious diseases like malaria and HIV, as well as vaccine preventable diseases like measles and polio. As a result, the prevention of other causes of child mortality has taken on even greater significance—necessitating a focused approach to realize further improvements in child survival.

Neural tube defects (NTD) prevention has long been proposed as a feasible and impactful opportunity to decrease the toll of birth defects and contribute to further reducing child mortality globally. NTD (which include spina bifida and anencephaly) affect the development of the brain and spine, and can lead to lifelong disability and early death. Most NTD are preventable through relatively simple nutritional interventions focused on improving folate status in the population, and specifically in women of reproductive age. Supplementation and population-level mandatory folic acid fortification have been effective in countries where they have been widely implemented; however, implementing these interventions globally has proven challenging mainly due to gaps in knowledge of the folate status of women in many countries; in understanding the global burden of NTD, as varying estimates exist and multiple methods have been used to ascertain burden; and in country capacity to assess and evaluate the effectiveness and safety of interventions aimed at reducing the risk of NTD. Understanding the current versus the ideal state of the science, technical capacity, and knowledge of both folate status and NTD burden is of critical importance to further NTD prevention efforts.

The Micronutrient Forum works to bridge discovery and delivery to contribute to improving the health of the world's population by providing a common ground and collaborative space for professionals, organizations and stakeholders who share an interest in reducing micronutrient malnutrition. The key tenets of the Micronutrient Forum are to foster dialogue and collaboration between researchers, policy-makers, program implementers and industry; promote the application of up-to-date research to improve the design and implementation of scalable programs; and support the identification of gaps in knowledge and evidence. The Micronutrient Forum, with support from the Bill & Melinda Gates Foundation, convened a technical consultation (*Folate Status in Women and Neural Tube Defect Prevention*) to develop a roadmap to better inform and prioritize investments in NTD prevention in low- and middle-income countries; help guide implementation efforts in terms of feasibility of interventions and the potential for acceleration; and identify the research and knowledge gaps that remain.

The consultation considered the magnitude of the problem, identified research and knowledge gaps; reviewed evidence-based interventions and laboratory harmonization capacity, and developed a roadmap for global action to advance NTD prevention in low- and middle-income countries.

This publication provides a summary of the technical and scientific conclusions of the consultation that can serve as a framework to accelerate and scale-up NTD prevention.

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Preface

The results of the *Technical Consultation: Folate Status in Women and Neural Tube Defect Prevention* reflect the commitment and significant contribution of the committee. The exemplary dedication and commitment of this multi-disciplinary cadre of independent, knowledgeable and unbiased global experts led to significant achievement and important new research to the fields of nutrition and birth defects prevention.

Committee members took on an important and challenging task. They were charged with identifying a practical roadmap to better inform and prioritize investments in NTD prevention in low- and middle-income countries; to help guide implementation efforts in terms of feasibility of interventions and the potential for acceleration; and to identify the research and knowledge gaps that remain. They tackled, head-on, key scientific and technical questions to lead us from what is *known* to what is *possible*. Critical analysis, thoughtful deliberations and discussion, and consideration of the inputs from invaluable experts served as the cornerstones of the committee's work. The committee's efforts were realized in the successful development of a framework to move from knowledge to action to accelerate and scale-up NTD prevention in low- and middle-income countries.

The timeline for the consultation was robust, requiring the work to be advanced with deliberate thought and intention. We met as a full committee twice, developed eight important and comprehensive technical documents, commissioned two works that greatly add to the fields of nutrition and birth defects, and engaged with a broad pool of external experts to ensure transparency, inclusiveness and a full complement of expert inputs.

We thank the committee for their commitment and dedication to moving this work forward to realize the objectives and more. We also gratefully acknowledge the Micronutrient Forum and the Bill & Melinda Gates Foundation for their support and guidance throughout this process.

We are honored to have served as the core steering committee of this technical consultation.

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ACRONYMS AND ABBREVIATIONS

B12	Vitamin B12
CDC	US Centers for Disease Control and Prevention
DALY	Disability adjusted life years
EAG	Expert advisory group
HIV	Human Immunodeficiency Virus
LMIC	Low- and middle-income countries
LSFF	Large-scale food fortification
MBA	Microbiologic Assay
MNF	Micronutrient Forum
NTD	Neural Tube Defect and Neural Tube Defects
NTP	United States National Toxicology Program
RBC	Red blood cell
SACN	United Kingdom's Scientific Advisory Committee on Nutrition
UK	United Kingdom
UN	United Nations
WHO	World Health Organization
WRA	Women of reproductive age

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Executive Summary

Between December 2016 and April 2017, the Micronutrient Forum convened a technical consultation on folate status in women and neural tube defect prevention.

The objectives of the consultation were to: develop a roadmap to better inform and prioritize investments in neural tube defect (NTD) prevention in low- and middle-income countries; help guide implementation efforts (in terms of feasibility of interventions and the potential for acceleration); and identify the research and knowledge gaps that remain (including addressing any questions on safety and efficacy of folic acid interventions). A multi-disciplinary group which included global experts in nutrition, clinical pediatrics, epidemiology, policy translation, public health program implementation, folate status assessment, economics, and industry was brought together twice in Ottawa, Canada, on the premises of the Forum's host organization, Nutrition International.

The committee produced eight technical papers focused on three primary areas: (1) Folate status assessment in women of reproductive age; (2) NTD burden and surveillance; and (3) Interventions for NTD prevention.

This report provides a summary for each technical paper, leading to the recommendations endorsed by the committee, as well as the proposed framework for a roadmap for action. This framework outlines options for action on folate status assessment and points a way forward to the development and implementation of a global action plan for NTD prevention, identifying common impediments, ways to overcome or minimize these impediments, and describing the basic building blocks necessary to move to action.

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Introduction

Neural tube defects (NTD), which include spina bifida and anencephaly, are severe birth defects that affect the development of the brain and spine, and can lead to lifelong disability and early death. There is a wide range in the prevalence of NTD around the world, with Asia and Africa showing the highest prevalence and stillbirth associated with NTD. The most recent estimates for 2015 point to 260,100 NTD-affected pregnancies worldwide, with an estimated prevalence ratio of 1.86 per 1,000 live births. NTD are among the most serious and common birth defects, and develop during the first 28 days of pregnancy—often before women know they are pregnant—making it crucial that interventions are in place before a pregnancy begins. Improving the folate status of women of reproductive age (WRA) through relatively simple and inexpensive nutritional interventions can help prevent a substantial number of NTD.

Folic acid fortification of foods (augmented by micronutrient supplementation when access to centrally processed foods is limited) is a proven prevention strategy to improve the folate status of WRA and greatly reduces the risk of having a NTD-affected pregnancy. However, there are challenges to moving NTD prevention forward at-scale, which include a scarcity of dedicated resources and a lack of coordinated global action in low- and middle-income countries (LMIC). In addition, there are some fundamental factors that have, so far, limited the efforts of many institutions and organizations dedicated to improving the folate status of WRA and NTD prevention. Some of these challenges are data and information based—there is a lack of global data on folate status of women and different estimates of how big the global NTD burden is. Other challenges are rooted in the science of assessment, with limited use and availability of reliable laboratory methods to assess folate status. Further challenges involve obstacles to implementation, such as delivering folic acid to populations, identifying low-cost methods to assess folate status, and monitoring NTD and other health outcomes. Finally, advancing NTD prevention in LMIC is largely dependent on political will—in most countries, NTD prevention efforts lack the political will necessary to move prevention forward.

Creating strong political will is critical if large scale NTD prevention efforts in LMIC are to succeed. This will require high-level interest in accelerating prevention among global stakeholders, strong science- and social-based advocacy at the regional and national levels, and ultimately, a strong public health partnership between nutrition and birth defects partners.

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Rationale

Many countries have made progress in reducing child mortality typically by reducing the impact of infectious diseases like malaria and HIV, and vaccine preventable diseases like polio and measles. What we have seen is that other causes of child mortality are becoming increasingly important, with birth defects now becoming a leading cause of morbidity and under-five death in many countries. For this reason, further improvements in child survival will depend on the ability to prevent birth defects.

Preventing NTD represents a significant opportunity to decrease the toll of birth defects and neonatal mortality globally. A large portion of NTD are preventable through relatively simple nutritional interventions that improve the folate status in the population in general, and among WRA in particular. However, implementing interventions globally has its challenges and addressing these challenges is necessary to accelerate and scale-up prevention. Specifically:

- *Current global data on folate status and NTD are lacking.* The folate status among women of reproductive age is virtually unknown in many countries. Effective birth defects surveillance is largely absent in many countries, and most available data are based on model estimations rather than local data. There is an urgent need to develop data collection systems and track these data to help guide investment in prevention efforts.
- *Obstacles and challenges in delivering folic acid to populations remain.* Because NTD develop very early in pregnancy, when most women are not aware they are pregnant, efforts to reduce the risk of having a NTD-affected pregnancy will require making sure the folate status of women is improved through interventions such as mandatory folic acid fortification of foods or daily folic acid supplementation when food fortification is not available. Although some fortification policies might exist in countries, few countries have implemented these interventions at large scale and in a sustained manner, and countries with the highest expected burden are not among them.
- *The use of reliable laboratory methods to assess folate status needs to be implemented.* Particular attention must be paid to quality assurance and replicability of methods used.
- *Better low-cost, field friendly methods and innovations are needed.* These methods and innovations are needed to assess folate status, deliver interventions for NTD prevention, and monitor NTD and other health outcomes. These innovations are especially necessary where the burden is high, the need great, and the resources scarce.

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Approach

The Bill & Melinda Gates Foundation provided support to the Micronutrient Forum to convene a technical consultation on *Folate Status in Women and Neural Tube Defects Prevention*. The consultation was charged with taking a multidisciplinary approach in addressing the challenges to advancing NTD prevention, paying particular attention to LMIC.

The goals of the technical consultation were to develop a roadmap for LMIC countries to better inform and prioritize investments in NTD prevention; to help guide implementation efforts in terms of feasibility of interventions and the potential for acceleration; and to identify the research and knowledge gaps that remain, including addressing any questions on safety and efficacy of folic acid interventions. [Scoping questions for the technical consultation can be found on the Micronutrient Forum website at <http://micronutrientforum.org/folate-consultation/>. A list of identified research and knowledge gaps can be found in Annex E.]

A core steering group¹ considered over 45 global experts for the committee, using a structured selection process. The result was a well-balanced, objective multi- and inter-disciplinary committee composed of global experts in nutrition, clinical pediatrics, epidemiology, policy translation, public health program implementation, folate status assessment, economics, and private industry. [A list of committee members and staff can be found in Annex A.] The committee was convened twice in-person and once by teleconference.

The committee met first on 8-9 December 2016, in Ottawa, Canada to consider global data and scientific evidence related to folate status in WRA and NTD prevention. They considered the extent of the global NTD burden; the effectiveness of known interventions to prevent NTD; and the gaps in knowledge and research of folate status, laboratory methods to assess folate status, and different approaches to NTD prevention. The committee identified the main technical and scientific areas of the framework for action, and identified key areas where more information and inputs were needed to advance the work. Committee members drafted the technical reports, external experts were engaged and additional works commissioned in support of the consultation.

¹ Lynn Bailey (University of Georgia), Lorenzo Botto (University of Utah School of Medicine), Ken Brown (Bill & Melinda Gates Foundation), Luz Maria De-Regil (Nutrition International), Homero Martinez (Micronutrient Forum), Aliko P. Weakland (Core Engagement).

APPROACH

In February 2017, the committee held a teleconference to hear from additional external experts about innovative technologies, advocacy and approaches to estimating the current global NTD burden.

On 12-13 April 2017, the committee met again in Ottawa, Canada to review and discuss the draft technical reports, identify options for action and craft a key decisions framework for implementing a roadmap to amplify and accelerate NTD prevention in LMIC.

A two-phased review process was conducted with subject matter experts (SME) and global stakeholder groups. The first phase of the review included SME review of each of the eight technical reports. Each report was assigned 1-3 peer reviewers. A total of 16 SME participated. The second phase was a review of the full draft of the technical report by relevant stakeholders. Twelve reviewers representing 11 stakeholder organizations participated. Each reviewer completed a structured assessment framework that included free-text feedback.

The committee considered all available scientific and technical evidence and a comprehensive set of technical reports and recommendations on how best to facilitate NTD prevention in LMIC.

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Technical Summary

The technical reports addressed issues across three thematic areas: (1) Folate status assessment of WRA; (2) NTD burden and surveillance; and (3) Interventions for NTD prevention. Each report produced a scientific paper that was submitted to an internationally-renowned peer reviewed journal, and will appear in a special edition. Provided here is a brief overview of the scope, approach and main conclusions for each technical report.

FOLATE STATUS ASSESSMENT OF WRA

1) Folate Status of Women of Reproductive Age as Basis of NTD Risk Assessment

Scope: Acknowledging that the folate status of WRA is foundational to NTD prevention, the consultation sought to provide guidance regarding how folate status assessment in WRA can be used to predict NTD burden. The report encompasses a synopsis of evidence related to select folate status biomarkers; a differentiation between classical folate “deficiency” and folate “insufficiency” as a basis of NTD risk assessment based on assay-matched cut-offs; and examples of how the application of the WHO guideline for optimal blood folate can be applied in LMIC as a basis for new or evaluating current folic acid intervention programs designed to prevent NTD.

Approach: This section focuses on red blood cell (RBC) folate concentration and the rationale for the selection of this key biomarker by WHO as a validated indicator of NTD risk within a population. A framework for global assessment of folate status in WRA was provided by the WHO 2015 Guideline: *Optimal serum and red blood cell folate concentrations in women of reproductive age for prevention of neural tube defects* that recommended RBC folate concentrations and the microbiological assay (MBA) as the preferred folate biomarker and analytical assay, respectively, for assessing folate status. The report also established a threshold for “optimal” RBC folate ($\rightarrow 906$ nmol/L) that can be used at the population level to determine the need for, and guide monitoring and evaluation of, the impact of nutrition interventions designed to enhance folate status and prevent folic acid sensitive NTD. This threshold value is not a mean or median value but is the lowest end of the RBC folate distribution above which all women in the population should exceed to achieve optimal NTD risk reduction. Consistency in the estimated “optimal” RBC folate concentration predictive of NTD risk in the original study on which the WHO recommendation was based, and in subsequent modeling studies in other populations, supports the generalizability of this biomarker across populations with different racial groups and exposure to folic acid. Further, it was noted that

for data obtained with the contemporary MBA using 5-methylTHF rather than folic acid as the assay calibrator, an optimal RBC folate concentration for NTD risk reduction was determined to be $\rightarrow 748$ nmol/L. Therefore, in using the MBA for determination of RBC folate concentration as the biomarker for NTD risk assessment, it is important to apply assay-matched cut-offs for folate insufficiency. This was done for recent population-based surveys in two low- and middle-income countries, Guatemala and Belize, with the study results indicating that despite fortification efforts, there is an almost 50% prevalence and high demographic and regional variation in folate insufficiency in these countries, with highest prevalence in poor, rural and indigenous subpopulations. This suggests that in addition to population-based surveys to assess RBC folate concentrations in WRA, future intervention efforts need to include surveillance to monitor trends in folate status and NTD prevalence to confirm that programs are reaching the population subgroups most at risk. Although NTD risk cannot currently be estimated based solely on serum/plasma folate concentration, deficient serum/plasma folate concentrations determined with the appropriate methodology would suggest a potential greater prevalence of RBC folate below the insufficiency threshold.

Conclusions: In summary, RBC folate concentration can be used to estimate the risk of NTD in population groups of WRA. To achieve the greatest reduction in NTD, an “optimal” RBC folate concentration defined as 906 nmol/L (or an assay adjusted cut-off) should be exceeded with RBC values below this threshold defined as “insufficient”. The analytical method of choice to measure RBC folate concentration is the MBA. For the global assessment of NTD risk, there is a need to “harmonize” the microbiological assay in selected laboratories conducting the RBC folate analysis.

2) Safety of Folic Acid

Scope: The safety of folic acid fortification remains a subject of some debate on the global stage. As such, it is of vital importance to maintain transparency and address this issue directly. The evidence for the safety of folic acid fortification was reviewed, based primarily on the very thorough assessments conducted by the US National Toxicology Program (NTP) in 2015 and the UK Scientific Advisory Committee on Nutrition (SACN) in 2016, and the published literature since these reports were released.

Approach: Neither the SACN nor the NTP reports identified conclusive evidence for adverse effects due to folic acid. The NTP report emphasizes the uncertainty that exists in the present literature, proposes a research agenda, and emphasizes that “additional work is critical to fully evaluating the known public health benefits of folic acid, as well as the potential – but still unevaluated – risks that may exist.” The UK Scientific Advisory Committee on Nutrition 2016 draft report reviewed literature published since their 2006 and 2009 recommendations for mandatory fortification of flour with folic acid.

Conclusions: Overall, the totality of the evidence of the literature fully supports the benefits of mandatory folic acid fortification in NTD prevention. Furthermore, there are no established risks for adverse consequences resulting from existing mandatory folic acid fortification programs that have been implemented in many countries. Current folic acid fortification programs have

been shown to support public health in populations, and the exposure levels are informed by, and adherent to, the precautionary principle. Additional research is needed to assess the health effects of folic acid supplement use when the current upper limit for folic acid is exceeded.

3) Should B12 be Considered in Assessing NTD Risk

Scope: There is a strong biological premise for considering vitamin B12 as well as folic acid in strategies for NTD prevention. This is based on the closely interlinked biochemical pathways involving these two vitamins. Thus, two possibilities were considered within the scope of this section: (1) that vitamin B12 might have an independent or synergistic role in NTD prevention, such that adding B12 in fortification programs might reduce NTD further than fortifying with folic acid alone; and (2) that reduction of B12 deficiency among women of reproductive age might have an important function in enhancing the capacity of folic acid to prevent NTD. The topic of including B12 in fortification programs to address adverse effects of high folic acid intake was outside the scope of this section because a discussion of safety concerns in relation to folic acid intake is covered elsewhere in the report. The purpose of this section was to consider two issues concerning the relationship of B12 in relation to NTD prevention: (1) whether B12 deficiency is an independent contributor to NTD risk; and (2) whether B12 should be delivered routinely along with folic acid to avoid possible masking of B12 deficiency.

Approach: The methods involved a detailed review of the existing literature on vitamin B12 and NTD to assemble all the available evidence and assess the quality of this evidence in supporting the strongest possible recommendation in relation to B12 fortification. Relevant evidence was available from observational studies, intervention studies and genetic association studies. Key findings are that, in contrast to the well-established role of folic acid in NTD prevention, the available evidence relating to vitamin B12 is largely limited to observational data on blood concentrations of the vitamin in NTD-affected women. Within this context, the strongest evidence supports the hypothesis that low maternal vitamin B12 status confers increased risk of having an NTD-affected pregnancy, both assessed separately and combined with risk from low blood folate status. These studies also suggest that the metabolic interaction between vitamin B12 and folate can create a synergy in relation to the magnitude of risk. Globally, there is ample evidence of widespread folate and/or vitamin B12 deficiencies in LMIC but there is also considerable divergence of vitamin B12 status across regions, likely due to genetic as well as nutritional factors. One key factor demonstrated in several studies is that having vitamin B12 deficiency presents an obstacle to achieving optimal red cell folate concentrations for prevention of NTD. This suggests that it would be wise to consider improving vitamin B12 status in conjunction with folic acid intervention to optimize the reduction of NTD but the efficacy of such a strategy in reality would have to be considered in the context of the prevalence of vitamin B12 deficiency in WRA across different populations and ethnic groups.

Conclusions: The known synergy between vitamin B12 and folate makes it highly probable that fortification with vitamin B12 will improve the efficacy of current folic acid fortification programs to prevent NTD. The case is much stronger in parts of the world where vitamin B12 status of women of reproductive age is low but even in high income countries, the probable

benefit outweighs any known negative consequences. In countries with a high prevalence of B12 deficiency, consideration of B12 inclusion with folic acid should be a top priority. More research is needed to establish the efficacy of low-dose B12 fortification, the potential interactions of vitamin B12 with microbiome and parasitic agents, and the influence of genetic variability on vitamin B12 status. It is not known how subtle alterations in vitamin B12 status might change the equilibrium that exists between the human host and gastrointestinal parasites or how much B12 should be included in a fortification program to optimize improvement in status and to ensure that no adverse interaction with infectious parasites are promoted. Further B12 intervention studies in women of reproductive age in different nutritional and background parasitic disease settings therefore constitutes a major research need.

4) Framework for Laboratory Harmonization of RBC Folate Measurements in LMIC and Regions

Scope: This technical section describes the challenges in assessing folate status, both from an analytical and a data interpretation standpoint. It also lays out a framework for laboratory harmonization of folate measurements using the microbiologic assay set up in a network of regional resource laboratories.

Approach: Folate methods show poor comparability even within the same analytical technique, but particularly among different platforms of protein-binding assays. This poses significant data interpretation challenges for comparisons among studies, sometimes also for longitudinal assessments in the same population. It also complicates the correct use of existing cut-off values and the interpretation of the resulting prevalence estimates to describe folate status. For these reasons, a designated folate assay has to be chosen that can be reliably set up and maintained in selected LMIC laboratories. The microbiologic assay satisfies those criteria. There is a limited need for blood folate measurements in a LMIC because of the periodic nature of surveys. Thus, having individual country laboratories that assess folate status for population surveys may not be sustainable, and having reference regionalized laboratories makes more sense.

Conclusions: The microbiologic assay needs to be harmonized through the use of common critical reagents, most importantly the folate calibrator and microorganism, so that it can be used in LMIC to assess folate status in populations. The availability of a microbiologic assay kit that contains these critical reagents would greatly facilitate laboratory operations. Having a network of regional resource laboratories that are proficient in conducting the folate microbiologic assay and willing and able to perform service work for other countries could be a sustainable way to create an infrastructure where qualified laboratories produce reliable blood folate data. Each resource laboratory needs to undergo an annual evaluation and certification to verify and document the laboratory's achievement and maintenance of proficiency in conducting the folate microbiologic assay. This ensures comparability of results across laboratories and over time and allows the use of the same cut-off values to describe folate status in different populations.

NTD BURDEN AND SURVEILLANCE

5) Global Burden of NTD

Scope: Neural tube defects (NTD) affect births worldwide and cause life-long disability among those who survive. NTD are also associated with increased risk of stillbirths, and are indicated in a disproportionately high number of neonatal, infant, and under-five deaths compared to unaffected births. It is widely recognized that studies and estimates on the prevalence of NTD burden vary globally, and that prevalence of NTD is proportionally greater in LMIC compared to high-income countries. Poverty and nutritional inadequacies in LMIC are known to increase the prevalence of NTD significantly. Folic acid is known to prevent a majority of NTD. Knowledge of current burden of NTD is lacking. We examined aspects related to measurement of prevalence of NTD globally and sources of variability in published literature. We also estimated the global prevalence of NTD for year 2015 using updated information from birth defects registries and current literature.

Approach: As our first aim, we reviewed historical and recent studies on NTD and addressed data quality issues in measuring the prevalence of NTD. In our review, we found that over 80% of countries worldwide have NTD prevalence rates above the expected baseline level 0.5 per 1,000 live births. The highest prevalence of NTD occurs in low- and middle-income countries, which lack resources for primary, secondary and tertiary prevention interventions. There is a wide variability in prevalence estimates both globally and within countries. Surveillance methods and existing risk factors (e.g. geographic or socio-economic variability, availability and use of folic acid, racial-ethnic and genotypic factors) were identified as potential sources of variability in prevalence of NTD. Additionally, missing data, limitations in access to care, and poor quality of surveillance studies contributed to under-ascertainment of prevalence. Similarly, there is limited knowledge on mortality associated with NTD as most countries do not measure this outcome systematically. As a second aim, we estimated the current global and regional prevalence of NTD and their uncertainty ranges for the year 2015, for 195 countries. All estimates were generated at a national level by applying the steps of the compartmental model in sequence to the estimated live births to generate estimated numbers affected for the year 2015. The main findings include that there were an estimated 260,100 NTD-affected pregnancies worldwide in 2015, with an NTD prevalence ratio of 1.86 per 1,000 live births. Also, it was found that the prevalence varies by UN sub-region, ranging between 0.75 and 3.10 per 1,000 live births. Asia and Africa have the highest prevalence and stillbirths associated with NTD.

Conclusions: The estimated global prevalence of NTD-affected pregnancies is large and the number of pregnancies affected with this preventable birth defect are continuing to occur in hundreds of thousands all over the world, disproportionately impacting families in impoverished countries. NTD are invisible to policy-makers, and yet have a significant emotional and economic impact on families and society, while also contributing to loss of human potential for countries. We recommend that countries invest in prevention of NTD through proven NTD prevention programs. Well-designed population-based birth defects surveillance systems that examine all pregnancy outcomes (including live births, stillbirths and elective terminations for fetal anomalies) are necessary to understand the total prevalence of NTD in a country, and

also to evaluate prevention programs. Blood folate surveys among women of reproductive age can also be used as a strategy to predict the NTD burden. Improving health care resources in developing countries can prevent child mortality associated with NTD-affected pregnancies, and contribute towards achieving Sustainable Development Goals on reductions in neonatal and under-five mortality. We have the potential to prevent a large number of NTD-affected pregnancies with mandatory fortification with folic acid. Given the appropriate resources and public health infrastructure and commitment, it should be possible to accelerate surveillance of NTD and their prevention.

6) Rethinking Surveillance for NTD Prevention

Scope: Reliable and ongoing systems to assess and track NTD occurrence and related health burden are lacking in most LMIC. There is a need for robust population-based tracking systems that capture all pregnancy outcomes using multiple data sources. A framework for surveillance specifically targeted at supporting and accelerating NTD prevention was considered. By providing actual, reliable estimates of the burden of disease and of the benefits of prevention, surveillance can help increase awareness, inform policies, and track the effect of interventions such as folic acid fortification. Accurate and timely data must drive action.

Approach: There is a strong practical argument for concurrent assessment and tracking of the health impact of NTD (e.g. birth prevalence and survival) together with its main cause, the degree of folate insufficiency in the population. However, a review of available information shows how many LMIC lack such data and the registration systems needed to reliably generate these data on an ongoing basis (a basic tenet of health surveillance). In addition to the scarcity of reliable data systems (including at times even basic vital/civil registration of births and deaths), challenges to health surveillance in many LMIC include low visibility of NTD (and birth defects in general) in the overall context of childhood health priorities; variable but often high numbers of home births and out-of-facility health care; and limited capacity and technical training in NTD surveillance and care.

Conclusions: For greater effectiveness, NTD prevention activities such as fortification need to incorporate an element of ongoing assessment, to demonstrate benefits as well as remaining gaps. The ideal system (“triple surveillance”) would integrate population surveillance of blood folate levels, of NTD birth prevalence (among all pregnancy outcomes), and health outcomes in children born with NTD (e.g. below target effectiveness, missed population subgroups). Depending on available resources and systems, individual countries may be at different stages of preparedness and ability to implement such surveillance. Successful deployment of effective surveillance will require several elements: adapting surveillance to local priorities and systems; focusing on key data (and avoiding “recreational data collection”); maximally leveraging existing health care and data systems; showing the usefulness of the data for prevention and care; devising innovative approaches (e.g. population sample surveys); and developing regional expertise and networks to help build and leverage high-end skills (e.g. clinical case review, epidemiologic analysis) and share findings. Rethinking surveillance with the goal of prevention has the potential of accelerating the pace as well as lowering the cost of prevention.

INTERVENTIONS FOR NTD PREVENTION

7) A Public Health Approach to Prevention of NTD: Folic Acid Fortification

Scope: Food fortification with folic acid is a proven solution with potential to cover the majority of the population in many countries. However, much work is needed to build new programs and to improve industry compliance and effective coverage of existing programs. Information is needed on the reach and effectiveness of folic acid fortification, and novel approaches should be considered to reach WRA either through new fortification vehicles or other technologies where high coverage is not achievable through current programs. Proven interventions for NTD prevention were evaluated and effective approaches to scale-up these interventions considered, as well as a snapshot of potential innovations that require further research. The challenges of folic acid supplementation are summarized; details on the global situation and gaps of large-scale food fortification with folic acid – in particular the fortification of maize meal and wheat flour – are provided; opportunities to prevent NTD through rice fortification with folic acid were considered. Research gaps and public health policy concerns related to the potential folic acid fortification of additional commodities (e.g. salt, sugar, etc) to expand the reach to WRA were considered.

Approach: A review of the status of folic acid interventions was completed using secondary data sources. The published literature on the impact of folic acid fortification programs were reviewed and summarized. The findings show that large-scale food fortification (LSFF) with folic acid is a cost-effective, evidence-based intervention that reduces NTD. In addition, it was found that LSFF can complement long-term nutrition-specific and nutrition-sensitive strategies to strengthen food systems; it also increases nutritional diversity and addresses nutrient deficiencies. While the trend to establish national mandatory folic acid fortification programs has led to over 80 countries mandating this intervention, there remain three critical gaps which need to be addressed to ensure that LSFF is fully utilized in LMIC to prevent NTD moving forward. These are: (1) the need to “build and expand” the enabling environment and expand programs where there is currently no legislation; (2) the necessity to “improve” low quality on existing programs; and (3) the need to measure and sustain programs by generating new coverage data and evidence of impact in LMIC.

Conclusions: The overarching conclusion is that LSFF should be a component of most national public health strategies and certainly where: (1) existing food supplies and limited access to nutritious foods fail to provide adequate levels of folate in the diet; and (2) there is a fortifiable food vehicle consumed regularly by the majority of the population and that is processed by centralized industry. There is much work to undertake still to build the enabling environment and expand programs where there is currently no legislation; to “improve” the low quality of delivery of existing programs; and to measure and sustain programs by generating new coverage data and evidence of impact in LMIC. Finally, considering the coverage limitations of fortifiable cereal grains in many countries, it is important to invest in further research of new vehicles (e.g. salt, bouillon cubes, sugar, fish sauce, biofortified crops) to enhance scale-up of the delivery of folic acid to those who need improved intakes.

8) The Investment Case for Folic Acid Fortification

Scope: Securing resources for NTD prevention remains a major hurdle at national and global levels and will depend heavily on making the investment case for NTD prevention in LMIC to national and global stakeholders. There is compelling evidence that NTD can be prevented through mandatory folic acid fortification. Why then is an “investment case” needed? At the core of the answer to this question is the notion that governments and individuals have limited resources on which there are many competing claims. An investment case compares the costs and benefits of folic acid fortification relative to alternative life-saving investments and informs estimates of the financing required for implementation.

Approach: We assessed these costs and benefits through estimates of the cost per death averted and Disability Adjusted Life Years (DALY). Our best estimate is that the cost per death averted through mandatory folic acid fortification is \$957 and the cost per DALY is \$14.90. Both compare favorably against recommended life-saving interventions such as the rotavirus vaccine and insecticide treated bed nets. We estimate that over 10 years, 50,000 NTD-related deaths would be averted at a cost of approximately \$43 million USD.

Conclusions: There is a strong economic argument for mandatory folic acid fortification. It is likely that folic acid fortification will yield a positive return on investment for societies and prevent thousands of preventable child deaths. More precise estimates will require better data on the costs of implementing fortification and on the costs of improving compliance where regulations are already in place.

COMMISSIONED WORKS

In addition to the foregoing technical reports, the consultation commissioned the following two review papers:

1) Systematic Review of Folate Status of Women of Reproductive Age

A partner collaboration group² was established through the consultation to conduct a systematic review of the current evidence on folate status of WRA. This review will help inform global NTD prevention efforts and monitoring and evaluating impact. This work is in process and is expected to be completed in the autumn of 2017.

2) Global Estimates of NTD Burden

Following the committee’s assessment that the published reports on global NTD burden are extremely variable and based on inconsistent methods and spotty data, global experts³ were commissioned to develop and execute a rigorous method to re-estimate the current global burden of NTD and determine the confidence range of these estimates. This work is in process and is expected to be completed in the autumn of 2017. Preliminary estimates for 2015 point to 260,100 NTD-affected pregnancies worldwide, with an estimated prevalence ratio of 1.86 per 1,000 live births.

² CDC, Nutrition International, University of Georgia, Micronutrient Forum, WHO

³ Dr. Hannah Blencowe, Maternal Adolescent Reproductive and Child Health Centre, London School of Hygiene and Tropical Medicine, London, England

6

Framework For Action: Advancing And Accelerating NTD Prevention

After considering all the technical and scientific evidence, the committee developed a conceptual framework as a basis for preparing a global Roadmap for Action to assess folate status in WRA and develop an action plan for NTD prevention in LMIC. This framework aims to better inform and prioritize investments in NTD prevention, help guide implementation, and identify research and knowledge gaps that remain.

The framework aims to (1) define options for action on folate status assessment and (2) outline a way forward to develop and implement a time-bound global action plan for NTD prevention. Table 1. provides an overview of the common impediments to action of NTD prevention, ways to overcome or minimize these impediments and frame action, and the basic building blocks necessary to move forward in LMIC.

It is important to note that this framework identifies common impediments to action to NTD prevention, ways to overcome or minimize these impediments and frame action, and the basic building blocks necessary to move to action in LMIC. The framework provides a way forward toward implementing a global action plan as identified through the technical consultation where a key decisions framework was considered focusing on strategy (how to drive the roadmap), people (who are needed to realize the strategy), execution (how to move forward), and funding (where support could be directed). This framework does not present a complete global action plan, as it does not provide specific strategic objectives, a timeline for achieving these objectives or specific roles and tasks to be taken by stakeholder groups.

THE CHALLENGE IN FOLATE STATUS ASSESSMENT, NTD SURVEILLANCE AND INTERVENTIONS

One of the first considerations in developing the framework was to identify the common technical, market, economic, resource and political impediments for NTD prevention in LMIC. Tables 1-3 provide a list of acknowledged challenges in the areas of folate status assessment, NTD surveillance, and interventions to prevent NTD.

Table 1. Impediments to action

FOLATE STATUS ASSESSMENT	
Assumptions	
The folate status of women of reproductive age is foundational to NTD prevention	
Folate insufficiency based on Red Blood Cell folate predicts NTD risk	
Microbiologic Assay (MBA) analytical method must be used to define folate insufficiency	
Population-based surveys in LMIC illustrate impact of income/culture/location on folate insufficiency and NTD risk (the efficacy of folic acid intervention programs are dependent on this information)	
Topline Impediments to Action in LMIC	
Technical	Inadequate technical expertise regarding field activities, lab measurement, quality assurance, interpretation and data analysis
	Inadequate number of laboratories conducting recommended microbiologic method
Resources	Inadequate laboratory equipment
	Difficulty procuring necessary supplies
	Difficulty hiring and retaining qualified staff
	No budget allocated for nutritional surveillance
Political & Legal	Transfer of specimens and data between laboratories
	Geopolitical positions
	Delayed access to data to monitor public health progress
	Advocate for action and investment
NTD SURVEILLANCE	
Topline Impediments to Action in LMIC	
Technical	Limited expertise
	Limited or no civil registration (births, deaths)
	Few resources
	Competing needs (high mortality for other health issues)
	No data for advocacy
	Implementation and compliance issues with fortification
Market	Largest market impediment is limited incentives in surveillance (e.g. Will companies that are putting folate in food be interested?)
Political	Little to no interest
	Lack of appreciation on the value of NTD surveillance
	Competing priorities with more “visible” issues
	Lack of birth defects advocacy groups or champions

Table 1 continued next page

Table 1. Impediments to action (continued)

INTERVENTIONS	
Topline Impediments to Action in LMIC	
Technical	Limited knowledge and capacity among industry and government
	Limited infrastructure
	Lack of pre- and post-surveillance in the health, food and medical arenas
Economics and Behavior	Fragmentation of food processing industry
	Economic viability
	Consumer behavior and education
Political	Fraud and petty corruption
	Challenges with prioritization
	Lack of leaders and champions
	Limited to no budget availability
	Absence of legal frameworks to mandate fortification
	Limited capacity to monitor or assure industry compliance with fortification standards
Infrastructure availability	The importance of civil society organizations in driving political will
	Limited availability of birth clinics
	Shortage of trained health workers to assess NTD
	High prevalence of non-institution-based births (e.g. home births)

WAYS TO OVERCOME CHALLENGES AND TO FRAME ACTION

Once the top-line challenges to moving NTD prevention forward in LMIC were noted, attention turned to crafting key strategies that could be used to overcome them. Figures 1-3 provide these key strategies.

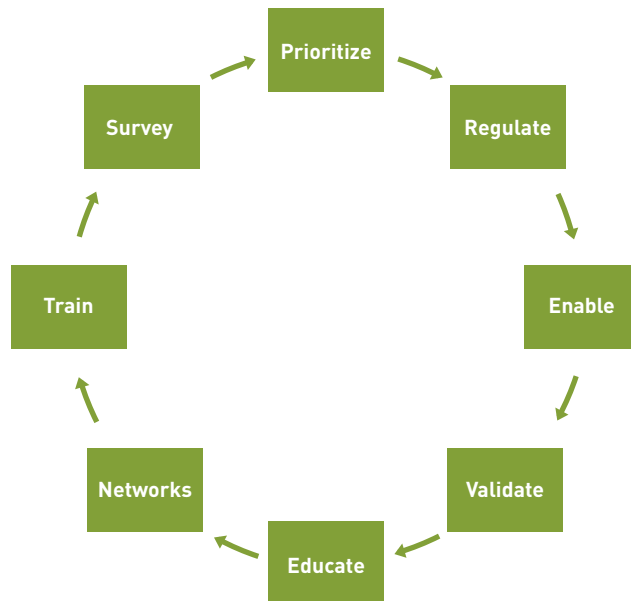
Figure 1. Overcoming challenges in folate assessment

Technical	Resources	Political & Legal
<ul style="list-style-type: none"> • Train for all aspects and availability of procedures • Make a microbiologic assay kit available to country laboratories • Continue efforts to develop simple field technologies • Build a network of regional labs to enhance capacity (train-the-trainers) 	<ul style="list-style-type: none"> • Engage in political advocacy with policy-makers to describe that status data is intermediate success measure for ultimate NTD reduction • Address key personnel issues such as ensuring that senior lab administrators have knowledge of laboratory sciences (pre- to post-analytical) and the administrative authority to make appropriate decisions 	<ul style="list-style-type: none"> • Build existing lab infrastructure • Provide examples of legal agreements for material transfers • Effectively plan to anticipate potential barriers • Consider advocating for investment and action to overcome the impediments

Figure 2. Framing surveillance action

Articulate workable options targeted to different local typologies	Focus on the value of high quality information	Take the long view and the short view
<ul style="list-style-type: none"> • Civil data/registration infrastructure (births, deaths), health care systems (providers and medical records), magnitude of home vs. hospital births, birth defect activities in place (surveillance, prevention, care) • General: pilot to test tools and processes, then assess and expand 	<ul style="list-style-type: none"> • Sampling design; good data from a few areas is better than lots of noisy/biased data from an entire country 	<ul style="list-style-type: none"> • Early deliverables: data for baseline and advocacy • Build for the future: countries transition to mature systems (more in-hospital births, better care leading to survival, higher priority for birth defect evaluation and interventions)

Figure 3. Overcoming impediments to prevention: A PREVENTS Approach

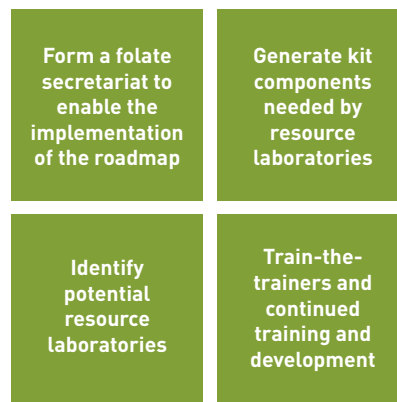


The translation of these actions is critically important. For example, “validate” concerns the issues around NTD but also those of food fortification; “network” refers to coordinating with and setting up multiple stakeholders; and “survey” concerns surveillance and monitoring.

MOVING TO ACTION

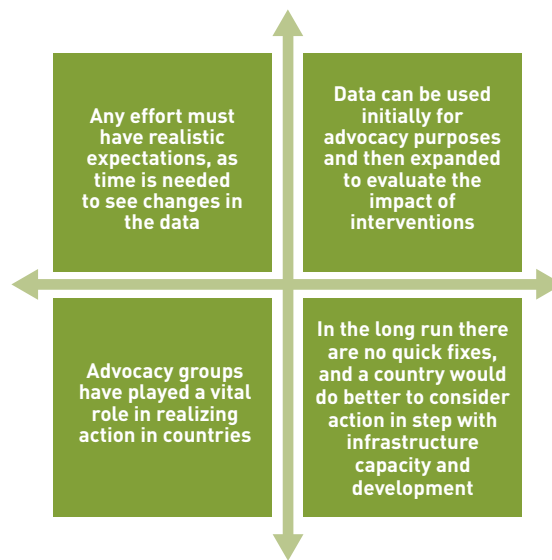
One of the key drivers to successful action is ensuring that the environment is ready to move action forward. Building on the key strategies to overcome challenges, Figures 4-6 illustrate the necessary building blocks to move to action in LMIC. They consider each of the three primary areas of action: considering folate status assessment, NTD surveillance, and interventions to prevent NTD, and acknowledge some immediate action areas to consider when moving to action.

Figure 4. Moving to action: Folate status assessment



Implementation: Immediate action areas

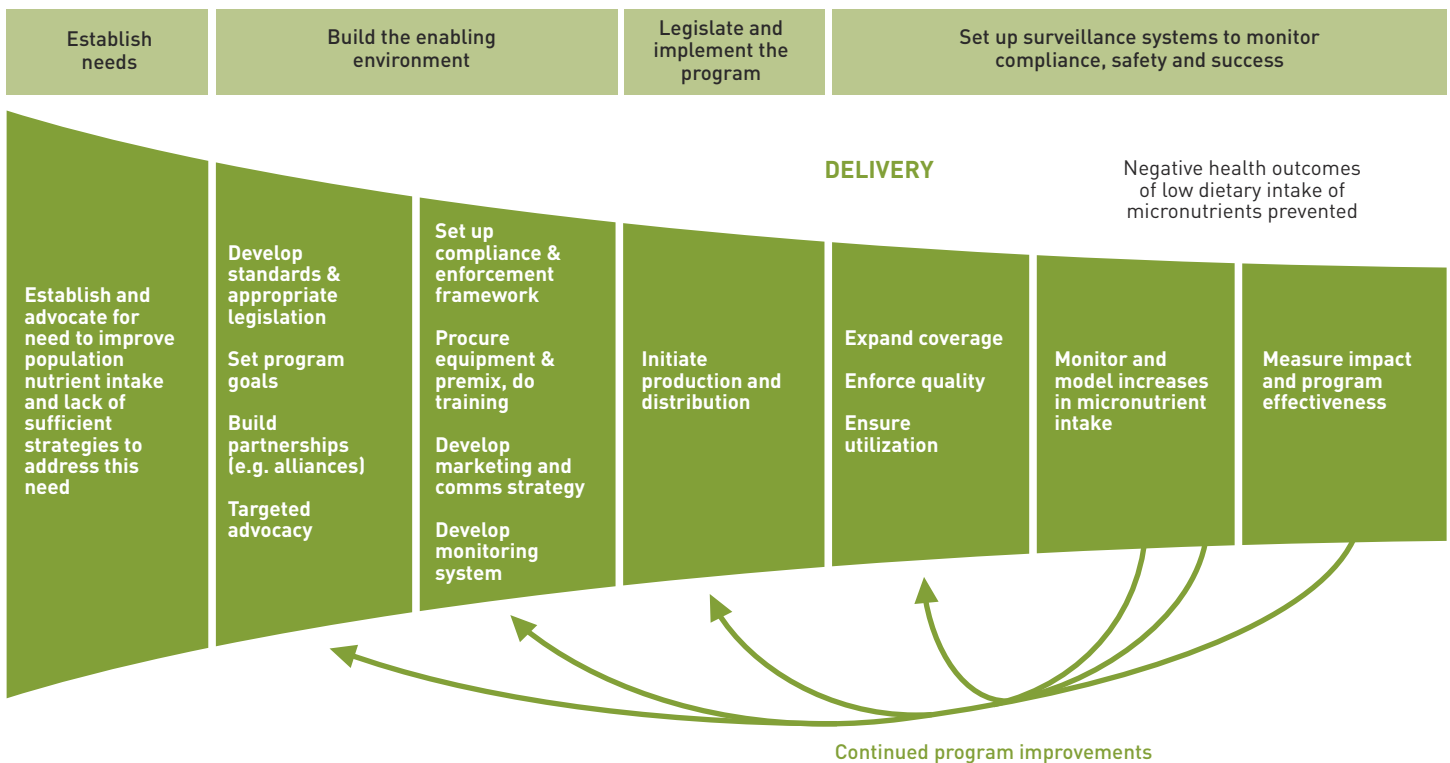
- Explore the need, feasibility (technical and political), costs, timeline, and management of a laboratory network
- Consider two laboratories per WHO region to help mitigate any political issues of sending samples between countries, and make the network more manageable
- Further consider what may be needed to include folate in nutritional assessments and whether support for harmonization of laboratory assessment should be broadened to general nutritional status and multiple micronutrients, rather than focused on folate assessment only

Figure 5. Moving to action: NTD surveillance**Implementation: Immediate action areas**

- Explore the need, feasibility (technical and political), costs, timeline, and management of NTD surveillance network
- Develop practical, tiered surveillance solutions addressing typical challenges in LMIC, including scarcity or lack of registration systems and health records, varying proportions of home births, lack of specialized medical training
- Explore innovative approaches to potential challenges, including use of population sampling, point-of-care photography and distance-based training to streamline the process and ensure quality
- Develop a regional network to share harmonized surveillance data and identify regional differences
- Explore collaborations with existing health surveillance systems (neonatal, pediatrics, nutritional, woman and child) to minimize start-up costs, promote sustainability and increase use of data for multiple stakeholders
- Build a process into surveillance for timely dissemination of information to support the advocacy agenda

Figure 6. Moving to action: Folate status assessment

The basic building blocks necessary to move to action in LMIC are to: establish a need; build the enabling environment; legislate; implement the programs; and set up surveillance systems to monitor compliance, safety and success.



Key assumptions

- The start point and trajectory of individual countries may be different depending on the country context
- Primary decisions and/or action items identified along the spectrum take into account that there is a series of feedback loops embedded in any process
- Though having good data on both NTD and folate status is important, countries could move forward with action, but should not lose sight of establishing a way to deliver on obtaining good data to help with monitoring and evaluating interventions

Implementation: Immediate action areas

- Consider any “quick wins” for fortification that could be mapped out and applied to prioritize countries where near term resources and efforts can be applied
- Assessment of country’s “state of readiness” is an important prioritization element
- Explore the minimum potential coverage of a fortification vehicle to motivate a related fortification program as well as the maximum number of production sites to reach an identified level of coverage
- Facilitate understanding of how best to guide countries in fortification vehicle selection including listing all appropriate vehicles for folic acid fortification and wed that with a technology agenda. Consider this step-wise approach: (1) Identify the feasibility of fortification; (2) Identify certain platforms that reach the target population; and (3) Explore potential pharmacologic or other technological approaches to delivering folic acid and related program feasibility.

Table 2. Options for action in LMIC—Overview

CHALLENGES	FOLATE STATUS	NTD SURVEILLANCE	INTERVENTIONS
<i>Technical</i>	Inadequate technical expertise regarding field activities; Laboratory measurement methods; Quality assurance; Accurate interpretation and data analysis; Inadequate number of laboratories conducting recommended microbiologic assay	Limited expertise; Limited or no civil registration (births, deaths); Few resources; Competing needs (high mortality for other health issues); No data for advocacy; Implementation and compliance issues with fortification	Knowledge and capacity among industry and government; Infrastructure; Lack of pre- and post-surveillance in the health, food and medical arenas
<i>Market, Economics & Behavior, Resources</i>	Inadequate laboratory equipment; Difficulty procuring necessary supplies; Difficulty hiring and retaining qualified staff; No budget allocated for nutritional surveillance	Largest market impediment is limited incentives in surveillance (e.g. Will companies that are putting folate in food be interested?)	Fragmentation of food processing industry; Economic viability; Consumer behavior and education
<i>Political & Legal</i>	Transfer of specimens and data between laboratories; Geopolitical positions; Delayed access to data to monitor public health progress; Advocate for action and investment	Little to no interest; Lack of appreciation on the value of NTD surveillance; Competing priorities with more “visible” issues; Lack of birth defects advocacy groups or champions	Fraud and petty corruption; Challenges with prioritization; Lack of leaders and champions; Limited to no budget availability; Legal frameworks

Table 2 continued next page

Table 2. Options for action in LMIC—Overview (continued)

OVERCOMING CHALLENGES & FRAMING ACTION	Folate Status	NTD Surveillance	Interventions
	<ul style="list-style-type: none"> • Train for all aspects and availability of procedures • Make a microbiologic assay kit available to country laboratories • Continue efforts to develop simple field technologies • Build a network of regional labs to enhance capacity (train-the-trainers) • Engage in political advocacy with policy makers to describe that status data is intermediate success measure for ultimate NTD reduction • Address key personnel issues such as ensuring that senior lab administrators have knowledge of laboratory sciences (pre- to post-analytical) and the administrative authority to make appropriate decisions • Build existing lab infrastructure • Provide examples of legal agreements for materials transfers • Effectively plan to anticipate potential barriers • Consider advocating for investment and action to overcome the impediments 	<p>Articulate workable options targeted to different local typologies:</p> <ul style="list-style-type: none"> • Civil data/registration infrastructure (birth, deaths), health care systems (providers and medical records), magnitude of home vs. hospital births, birth defect activities in place (surveillance, prevention, care) • General: pilot to test tools and processes, then assess and expand <p>Focus on the value of high quality information:</p> <ul style="list-style-type: none"> • Sampling design; good data from a few areas is better than lots of noisy/ biased data from an entire country <p>Take the long view as well as the short view:</p> <ul style="list-style-type: none"> • Early deliverables: data for baseline and advocacy • Build for the future: countries transition to mature systems (more in-hospital births, better care leading to survival, higher priority for birth defect evaluation and interventions) 	<p>“PREVENTS”</p> <p>Prioritize; Regulate; Enable; Validate; Educate; Networks; Train; Survey</p> <p>The translation of these actions is critically important. E.g. Validate concerns the issues around NTD but also those of food fortification; Network refers to coordinating with and setting up multiple stakeholders; and Survey concerns surveillance and monitoring</p>
MOVING TO ACTION	Folate Status	NTD Surveillance	Interventions
	Form a folate secretariat to enable the implementation of the roadmap	Any effort must have realistic expectations, as time is needed to see changes in the data	Establish a need
	Generate kit components needed by resource laboratories	Data can be used initially for advocacy purposes and then expanded to evaluate the impact of interventions	Build the enabling environment
	Identifying potential resource laboratories	Advocacy groups have played a vital role in realizing action in countries	Legislate
	Train-the-trainers and continued training and development	In the long run, there are no quick fixes and a country would do better to consider action in step with infrastructure capacity and development	Implement the programs
			Set up surveillance systems to monitor compliance, safety and success

Table 2 continued next page

Table 2. Options for action in LMIC—Overview (continued)

ROADMAP IMPLEMENTATION: IMMEDIATE ACTION AREAS	Folate Status	NTD Surveillance	Interventions
	Explore the need, feasibility (technical and political), costs, timeline, and management of a laboratory network	Explore the need, feasibility (technical and political), costs, timeline, and management of NTD surveillance network	Consider any “quick wins” for fortification that could be mapped out and applied to prioritize countries where near term resources and efforts can be applied
		Develop practical, tiered surveillance solutions addressing typical challenges in LMIC, including scarcity or lack of registration systems and health records, varying proportions of home births, lack of specialized medical training	Assessment of country’s “state of readiness” is an important prioritization element
	Consider two laboratories per WHO region to help assuage any political issues of sending samples between countries and make the network more manageable	Explore innovative approaches to potential challenges, including use of population sampling, point-of-care photography, distance-based training to streamline the process and ensure quality	Explore the minimum potential coverage of a fortification vehicle to motivate a related fortification program as well as the maximum number of production sites to reach an identified level of coverage
	Further consider what may be needed to include folate in nutritional assessments and whether support for harmonization of laboratory assessment should be broadened to general nutritional status and multiple micronutrients, rather than focused on folate assessment only	Explore collaborations with existing health surveillance systems (neonatal, pediatrics, nutritional, woman and child) to minimize start-up costs, promote sustainability, and increase use of data for multiple stakeholders	Facilitate understanding of how best to guide countries in fortification vehicle selection including listing all appropriate vehicles for folic acid fortification and wed that with a technology agenda. Consider this step-wise approach: (1) Identify the feasibility of fortification; (2) Identify certain platforms that reach the target population; and (3) Explore potential pharmacologic or other technological approaches to delivering folic acid and related program feasibility
		Develop a regional network to share harmonized surveillance data and identify regional differences	
		Build a process into surveillance for timely dissemination of information to support the advocacy agenda	

7

Roadmap For Action: Prioritizing Investments In NTD Prevention

Using the information in the Framework for Action, the committee developed a Roadmap for Action, which outlines a time-bound global action plan for NTD prevention. Thinking through how best to implement the roadmap was an integral part of the consultation deliberations. The committee used a key decisions framework to consider strategy, people, execution and funding. Committee members concluded that it is necessary to develop an implementation strategy with a strong technical focus, and to establish a Folate Secretariat, Steering Committee and Expert Advisory Group (EAG) to coordinate a global action plan.

Implementing the Roadmap for Action and advancing NTD prevention research and program agendas requires a common understanding of the following key principles:

- a) Implementation of the Roadmap for Action will focus on NTD prevention in LMIC
- b) Harmonization within and among countries/regions should be pursued to maximize and leverage resources, strengthen impact, and advance a standardized approach to prevention where appropriate (e.g. folate assessment methods; advocacy; donor engagement)
- c) Coherent prevention programs using evidence-based interventions are the touchstones of implementation
 - i. Advancing proven interventions like fortification of appropriate food vehicles to achieve maximum effective coverage
 - ii. Exploring new and innovative strategies when existing strategies are unlikely to be successful
 - iii. Identifying new entry points for prevention is essential for acceleration and sustainability of prevention efforts
- d) Engagement with national-level stakeholders is paramount for success
 - iv. Providing a toolbox of options that can be tailored to specific country needs and capacity is crucial
- e) Securing additional donor engagement is necessary to support the coordinating committee and national activities, including advocacy for national investments
- f) Effective coordination and collaboration with existing and new partners to achieve common goals is critical

The committee proposes the implementation strategy be advanced in two phases.

Phase 1 would establish the Folate Secretariat and EAG to advance the roadmap by promoting activities on both global and national scales. The core concept of Phase 1 is to establish a group with technical expertise to leverage influence, align funding and program implementation, and to tap into important existing networks.

Phase 2 would consist of global and national actions, focusing on creating and disseminating “global public goods” (e.g. scientific advocacy, technical support, program and research priorities) around the consequences of folate insufficiency and fortification. The national component would prioritize LMIC for intervention options based on country interest; willing implementation partners; population size; regional representation (i.e. Africa and Asia); and countries with or without policies for mandatory fortification and existing programs.

The committee identified a list of priority funding actions to help advance the Roadmap for Action and help manage and coordinate the work. Two categories were identified for prioritized funding: (1) Operational priorities to advance the Roadmap for Action; and (2) Action priorities for an Expert Advisory Group.

1. **Operational Priorities for Advancing the Roadmap for Action:** Activating the framework will require infrastructure support to form a steering committee, establish and operate a Folate Secretariat, and coordinate and administer an EAG. Immediate action items and focus areas include:
 - a. Form a Steering Committee
 - b. Establish a Folate Secretariat to administer and coordinate an EAG with expertise in scientific advocacy (e.g. evidence synthesis, technical briefs); technical assistance (e.g. folate assessment and intervention design); surveillance, monitoring and evaluation; and research and program prioritization and oversight
2. **Action Priorities for Ensuing Expert Advisory Group:** Implementing recommendations from the EAG will help focus investments and direct research and program efforts. Immediate action items and focus areas include:
 - a. Laboratory Harmonization: Establish a network of resource laboratories for assessing folate status
 - b. Set a research agenda: Consider scientific evidence and aspects to including B12 in fortification (e.g. inclusion consideration/criteria, levels of fortification, efficacy studies); conduct research on efficacy/effectiveness of novel vehicles for folic acid fortification
 - c. Implementation: Assist with the design and implementation of model folate deficiency/NTD prevention programs in selected high-priority countries
 - i. Country selection may be based on population (manageability and impact) and the enabling environment (state of readiness for fortification, quality assurance, and the regulatory environment; existing tools including repository data to map the stage of readiness for fortification; and identification of potential global micronutrient actors)
 - d. Monitoring progress (folate status, outcomes, program coverage)

8

Conclusion

The estimated global prevalence of NTD-affected pregnancies is large and has a significant emotional and economic impact on families and society, while contributing to the loss of human potential for countries. However, NTD are often invisible to policy-makers. Economic estimates on cost per death averted through mandatory fortification and cost per Disability Adjusted Life Year both compare favorably when contrasted with recommended life-saving interventions such as the rotavirus vaccine and insecticide treated bed nets. There is an urgent need to implement the findings and conclusions of the technical consultation, and to advance and accelerate NTD prevention in LMIC. The need is clear. Effective prevention strategies exist to address the need. The Roadmap for Action provides a clear path forward to help direct and prioritize investments, advance resource mobilization, and garner the political will to accelerate NTD prevention in LMIC. There is very strong interest amongst the committee and various stakeholders to move this work forward, with the overarching priority being to implement the Roadmap for Action now.

REFERENCES

To view the full list of references go to:

<http://www.micronutrientforum.org/folate-references>

Annexes

Annex A: Committee of the Technical Consultation: Folate Status in Women and Neural Tube Defect Prevention

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Annex B: Committee Meeting Summaries

Meeting One: 8-9 December 2016

Objective: To consider the data and evidence related to folate status in women and NTD prevention. Examination included considering the magnitude of the global NTD burden; identifying knowledge gaps in both folate status assessment and methods harmonization and NTD prevention; reviewing the effectiveness of known interventions; and considering the pros, cons and challenges of different methodological approaches to NTD prevention.

Key technical issues addressed: The magnitude of folate inadequacy related to NTD risk and burden globally; whether the magnitude of folate inadequacy related to NTD risk is large enough to declare NTD a global public health problem; and what intervention options are available and/or possible to help address NTD in developing countries.

Teleconference: February 2017

Objective: To receive information from additional external experts in the areas of innovative technologies in private industry, advocacy and approaches to estimating global NTD burden.

Meeting Two: 12-13 April 2017

Objective: To review and discuss the draft technical sections of the roadmap report, further define options for action for low- and middle-income countries, and outline a key decision framework for implementing the Roadmap for Action post consultation.

Outcomes achieved: All sections were reviewed with respect to key findings, topline messages, facts and objectives, and related draft recommendations and consensus statements were reviewed. The committee identified options for action in low- and middle-income countries, and outlined a framework for global coordination and implementation of the roadmap after the consultation.

Annex C: Consultation Review Process

The committee reviewed and provided inputs on the content and all technical components of the Roadmap for Action. A two-phased review process was executed to ensure that the outcomes of the consultation represent a breadth and depth of expertise and inputs from global experts and stakeholder organizations.

Phase 1 of the review process was a Subject Matter Expert (SME) review of each of the technical components. A total of 16 SME reviewers were identified with inputs from the committee and the core steering group. Fifteen SME reviewers assessed one technical section, and one reviewer assessed two technical sections. Seven technical sections had two independent reviewers and one section had three independent reviewers.

Phase 2 of the review process was a stakeholder review. The stakeholder review consisted of 12 reviewers from 11 stakeholder organizations who were tasked with reviewing the complete report of the Roadmap for Action. The stakeholder review used an assessment framework to evaluate merit, organization, potential for impact and other criteria.

The Micronutrient Forum, the consultation committee and the core steering group thank all SME reviewers for their diligent, timely and robust technical reviews: Alireza Abbaspourrad, Robert J. Berry, Anne Lise Børke Monsen, Anje Brønstrup, Adolfo Correa, Lorna Cox, Krista Crider, Omar Dary, Boris Groisman, Susan Horton, Amanda MacFarlane, Scott Montgomery, Joseph Mulinare, Michelle Murphy, Jorge Rosenthal, Dylan Walters.

The Micronutrient Forum, the consultation committee and the core steering group thank the stakeholder organizations for their comprehensive review of the Report of the Roadmap for Action: Center for Spina Bifida Prevention, Rollins School of Public Health, Emory University; CDC-National Center on Birth Defects and Developmental Disabilities; CDC-National Center for Chronic Disease Prevention and Health Promotion; International Federation of Spina Bifida and Hydrocephalus; March of Dimes; Micronutrient Forum, Steering Committee; Nutrition International (Africa region); Nutrition International (India office); Scaling Up Nutrition; WHO-South-East Asia Regional Office – Newborn, Child and Adolescent Health; WHO-South-East Asia Regional Office – Nutrition.

All reviewers (SME and stakeholder) were asked to provide comments and constructive feedback, but were not asked to endorse the findings, conclusions and recommendations of this report or technical components. The review process was conducted uniformly and in a systematic way to maintain the integrity of the review process. The final responsibility of this report sits entirely with the Micronutrient Forum.

Annex D: Timeline (Consultation)

August - December 2016	January - April 2017	May - July 2017
<ul style="list-style-type: none"> • Form core steering group • Develop concept note and scoping questions • Identify, vet and solicit committee members • Finalize committee • Convene Meeting 1 	<ul style="list-style-type: none"> • Finalize Roadmap for Action development plan • Commission papers • Draft sections • Develop review protocol • Convene Meeting 2 • Revise sections 	<ul style="list-style-type: none"> • Draft Roadmap for Action • Execute review protocol: (1) Subject Matter Expert review; and (2) Stakeholder review • Finalize Roadmap for Action final report

Annex E: Research and Knowledge Gaps—Technical Areas

Research and Knowledge Gaps: NTD Burden

The following list includes important challenges and limitations that should be addressed to improve our knowledge of NTD burden.

1. There is scarcity of data on the prevalence of NTD in national populations, particularly for developing countries. Most countries, especially in Asia and Africa, lack birth defect surveillance systems.
2. Data that exist are of variable value because of lack of standardized methods. The use of standard case definitions and clinical criteria for classifying NTD that are reliable and valid across countries would allow comparison and examination of trends.
3. There is a need to develop new and improve existing surveillance systems for NTD to establish population-based, multi-source, and sustainable systems, while improving data quality by training and recruiting committed personnel.
4. There is need to understand and quantify all pregnancy outcomes affected by NTD. This includes assessment of stillbirths and elective terminations of pregnancy associated with NTD, as well as affected live births.
5. More data on mortality associated with NTD among live births are needed, including both early deaths in infancy and reduced life expectancy due to later deaths for which NTD contribute.

Research and Knowledge Gaps: Folate Status Assessment

Global harmonization of folate analyses

WHO guidelines recommend the MBA as the most reliable choice to measure RBC folate concentration as a basis of assessing NTD risk in a population. Most studies presented in the systematic review either used an alternative biomarker (serum or plasma folate), or there were differences in the analytical methods.

1. Due to these methodological issues, there is a critical need to develop a framework for laboratory harmonization of folate analytical measurements including the use of common critical reagents, trained laboratory personnel, development of MBA assay kits and folate certification programs for MBA assessment

Simplified statistical approaches

Modeling approaches used to-date for estimating NTD prevalence (i.e. NTD per 1,000 births) based on RBC folate concentrations are complex and require a trained statistician.

2. As this level of expertise may not be available in all LMIC conducting NTD risk assessment, simplified modeling approaches are needed and are currently in development

RBC folate concentration distribution as a basis of NTD risk

Although assay appropriate cut-offs for optimal RBC folate concentration may be useful for determining the overall prevalence of insufficiency, presentation of RBC folate concentration distributions (overall and possibly by subgroups) may also be important to identify subpopulations most at risk. Such data have not been included for most published studies in this area.

3. RBC folate concentration distributions (overall and possibly by subgroups) to identify subpopulations most at risk

Potential use of serum RBC folate concentration as biomarker for risk reduction

Although generally considered a biomarker of short-term folate status at the individual level, studies at the population level indicate that serum folate concentrations are reflective of both the degree of exposure to folic acid as well as the response to folic acid intervention. Serum folate has been used as the sole biomarker in many published studies from around the world assessing folate status in women of reproductive age. However, a threshold for the optimal folate status of populations for NTD risk reduction based on serum concentration has not been established. To use serum folate concentration in the assessment of NTD risk, it is necessary to first establish the relationship between serum folate and RBC folate concentrations and then use the “optimal” value for RBC folate concentration to determine the corresponding threshold for serum folate concentration.

4. Establish the relationship between serum folate and RBC folate concentrations and then use the “optimal” value for RBC folate concentration to determine the corresponding threshold for serum folate concentration

Inclusion of dietary information in folate status assessment

Although not essential for the implementation of a folic acid fortification program, when conducting population-based surveys to determine NTD risk based on RBC folate concentrations, it would be ideal to also include an appropriately performed dietary assessment. This would provide useful information regarding current sources of folate in the diet and food consumption patterns to identify best foods for fortification. Such an assessment should also provide information about current folic acid fortification programs including whether existing programs are “mandatory”, the specific staple(s) fortified, the amount of folic acid in the staple, contribution of fortified foods to the daily folate intake of women of reproductive age, and time of implementation of fortification in relation to conduct of folate status assessment, where possible, as to best inform appropriate “next steps”.

5. When conducting population-based surveys, determine NTD risk by including dietary assessment that incorporates detailed information on existing fortification programs

Appropriate selection of vehicle for fortification

High prevalence of folate insufficiency and wide variation by regional, socioeconomic and ethnic subpopulations have been reported in some countries with on-going folic acid fortification programs. Due to issues related to availability, affordability and acceptability wheat – and other fortified flours – may not be reaching those most vulnerable to low folate status; and as cereal staple preferences vary by cultural influences and dietary customs, a single fortified flour product may not be appropriate for an entire country or region. In addition to addressing immediate needs to improve folate status in women of reproductive age with established folic acid fortified food stuffs, fortification of a more universally accepted food staple such as salt or other condiments warrants investigation.

6. Investigating alternate vehicles for fortification

Updated systematic review of vitamin B12 status in LMI countries

7. An updated systematic review of worldwide vitamin B12 status seems warranted as a secondary priority to assessing folate status

Interaction of race and other factors with folate status and NTD risk

A paradox between folate status and NTD risk has been noted for non-Hispanic black women in the US which poses some interesting research questions including the following:

8. Since the vitamin B12 status of non-Hispanic black women is higher in comparison to non-Hispanic white women, does this significantly influence NTD risk?
9. Since the prevalence of the *MTHFR* TT genotype is lowest in non-Hispanic black women relative to other racial/ethnic groups in the US, how does this affect NTD risk in non-Hispanic blacks globally?
10. What type of interaction is there between the low folate status, high B12 status and low *MTHFR* TT prevalence related to NTD risk in non-Hispanic black women?
11. Are US non-Hispanic blacks unique or are they representative of blacks in other geographic regions such as LMIC, which would have overall lower B12 status?

Research and Knowledge Gaps: Surveillance

To drive evidence-based policies and maximize the effectiveness of interventions, countries will benefit from having reliable and timely information on 1) NTD prevalence; 2) the associated mortality/morbidity/disability; and 3) the magnitude and distribution of the causes (e.g. folate insufficiency) driving NTD prevalence. **Each country must assess its own set of needs and gaps.** The following general considerations may serve as a starting point.

1. Need for reliable surveillance data on NTD prevalence
 - a. Ideally on all affected births (live births, stillbirths, and where legal, pregnancy terminations)
 - b. From hospital as well as home births (the latter varies by country, but can be high)
 - c. Based on explicit and shared case definition
 - d. Generated through focused data gathering (no “recreational data collection”)
 - e. Conducted over time, regularly and in a timely manner, to track trends and assess the effectiveness of interventions (or lack thereof)
2. Need for reliable surveillance data on folate insufficiency and magnitude of other causes of NTD (including maternal diabetes and obesity)
 - a. Ideally on women of childbearing age
 - b. Measured objectively (e.g. blood folate concentration surveys, body mass index, etc.)
 - c. Ideally in the same population from which NTD cases originate, so that cause and effect can be linked
 - d. Repeated over time (timing to vary depending on exposure) to assess trends
3. Need for reliable surveillance data on health outcomes associated with NTD
 - a. Include survival, ideally beyond the neonatal and infant period
 - b. Expand when possible to morbidity and disability
4. Specific research questions:
 - a. NTD prevalence similar or different in the different LMIC, including countries in sub-Saharan Africa? How do actual rates compare to the estimated models used so far (e.g. in the March of Dimes report)?
 - b. Does the severity and distribution of NTD types correlate with the overall NTD prevalence?
 - c. What is the relation between blood folate concentration and NTD risk in populations outside of North America and China (where such relation has been evaluated)? Can blood folate concentration predict NTD risk and rates?
 - d. What is the impact of prenatal diagnosis on NTD rates and survival?
 - e. What is the current survival and morbidity associated with NTD in each country?

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5. System needs: reliable data come from stable, high quality systems. Needs vary by country, but some general considerations may be helpful in planning for system development and improvement
 - a. Commit for the long term: good programs take time to work and take root, and surveillance is meaningful if ongoing and sustainable
 - b. Provide training (and evaluate): especially related to systems management, clinical case review, coding and classification
 - c. Integrate surveillance in the clinical workflow: timeliness and cost can quickly degrade if birth defect surveillance is separate and independent of clinical workflow. Incorporating key elements of birth defects in existing clinical and public programs (including perinatal surveillance programs) decreases data abstraction and should improve speed and accuracy.
 - d. From the beginning, establish links (collaboration, data sharing) between birth defect surveillance and surveillance of outcomes/surveillance of risk factors.
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Research and Knowledge Gaps: Safety of Folic Acid

1. Classify those at risk for having a NTD-affected pregnancy. Although folic acid supplementation was shown to be efficacious in preventing NTD in controlled trials, a deeper understanding the fundamental biological mechanism linking folic acid intake to NTD risk reduction is needed to better target the intervention to those at risk, and further research is needed to potentially predict the role of folate in health and disease more broadly. This includes supporting ongoing genome-wide association (GWAS) studies to identify genetic risk alleles associated with risk for folic acid-responsive NTD, identifying environmental exposures that put women at risk for folic acid-responsive NTD, and fundamental science to elucidate the molecular pathways involved in neural tube closure defects.
 2. Conduct pre-clinical studies to determine if there is a dose-response relationship between folate status and/or folate/folic acid intake within the normal human exposure ranges and increased rates of tumor growth in appropriate animal and/or *in vitro* or *in silico* model systems.
 3. Conduct pre-clinical studies to test the hypothesis that conditions including age, pre-existing neoplasia, and/or genetics sensitize cells to cancers that are responsive to folic acid within exposure ranges observed in human populations. This could include choosing appropriate animal models to better understand the effects of the timing and exposure of folic acid on cancer outcomes, comparing the effects of folic acid and reduced folates, and of understanding dose-response relationship. Studies should compare effects of adequate folate status to those with elevated status at levels consistent with human exposures, and avoid comparisons to folate-deficient models.
 4. Pre-clinical studies are needed to determine if and how elevated folic acid intake exacerbates vitamin B12 deficiency at the level of metabolism, cellular physiology and human pathogenesis as there are very limited data from *in vitro* or animal models supporting the human observational data.
 5. Pre-clinical studies are needed to determine if folic acid functions in biological pathways leading to asthma sensitization or risk for diabetes. Rigorous controlled human studies in pregnant women and in children are needed to better assess if folic acid exposure during pregnancy and the post-natal period increases risk for asthma, allergy and diabetes.
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Research and Knowledge Gaps: Vitamin B12 in Fortification Programs

Dosage

1. Examining the optimal amount of vitamin B12 to add in a fortification program
2. Given NTD prevention as a primary outcome in relation to vitamin B12 status, intervention studies in women of reproductive age are an important research goal
3. Specifically addressing ensuring adequate B12 status for women entering pregnancy
4. More research is needed in relation to supplementing women of reproductive age in low vitamin B12 intake areas with folic acid but not vitamin B12 and specifically, whether fortification with B12 in low-income countries would counteract any real or perceived adverse metabolic effects.

Toxicity

5. Further research is needed on potential interactions between vitamin B12, the human microbiome and parasitic infections of the gastrointestinal tract to establish a beneficial regimen of fortification.

Research and Knowledge Gaps: Laboratory Harmonization

Most of the research gaps related to the framework of laboratory harmonization revolve around technical issues to simplify the maintenance, operation, and interpretation of the folate microbiologic assay.

1. Can a stable microbiologic assay kit be produced that can be stored refrigerated or even at ambient temperature for at least one year? This may include a lyophilized form of the microorganism that can be easily reactivated by dissolving in growth medium to generate the inoculum needed for a larger number of assays. Similarly, the use of a lyophilized calibrator could be explored. Lastly, the stable assay kit could contain pre-weighed quantities of other reagents that need to be added to the growth medium at the time of preparation.
2. Can the harmonized folate microbiologic assay achieve a comparable among-laboratory variability as a commercial protein-binding assay conducted on a single instrument platform?
3. Can folic acid (better stability) be used as a calibrator instead of 5-methylTHF if all laboratories use the same microorganism and results are mathematically adjusted to be equivalent to 5-methylTHF calibration?
4. Can RBC folate be accurately assessed from a whole blood folate measurement without having to separately measure serum folate and hematocrit and by using the available hemoglobin data?

Research and Knowledge Gaps: Fortification & Innovation

While there has been substantial progress scaling up this intervention, there remain three critical gaps which need to be addressed to ensure that mandatory LSFF with folic acid is fully utilized in LMIC moving forward: (1) the need to “build and expand” the enabling environment and expand programs where there is currently no legislation; (2) the necessity to “improve” low quality on existing programs; and (3) the need to measure and sustain programs by generating new coverage data and evidence of impact in LMIC. It is important to improve the availability of data on coverage and effectiveness and to understand the potential application of new food vehicles (e.g. salt, bouillon cubes, sugar, fish sauce, biofortified crops) to enhance scale-up of the delivery of folic acid to those who need improved intakes.

New vehicles

1. Does folate fortification of rice by metabolic engineering offer new avenues to significantly decrease NTD prevalence?
2. Does folic acid fortification of fish sauce in Vietnam offer opportunities to significantly improve intakes of folic acid?
3. Does folic acid fortification of salt and sugar offer opportunities to significantly improve intakes of folic acid?

Building an enabling environment for folic acid fortification

4. What are the drivers of political and business commitment for folic acid fortification and how can they be leveraged and constraints overcome?

Monitoring and enforcement of folic acid fortification

5. What combination of incentives and penalties can be applied to ensure folic acid fortification to standards, and what are their predicted effects?
6. What combination of regulatory monitoring improvements will lead to greater auditing and inspection of folic acid fortified foods, which will in turn improve compliance with relevant standards with the greatest cost-effectiveness?
7. What field-friendly technologies can be innovated or developed to better test levels of folic acid quantitatively in fortified foods and/or individuals consuming fortified foods?

Measurement of the coverage and effectiveness of folic acid fortification

8. What is the existing coverage rate of countries with mandated folic acid fortification programs?
9. How can existing industry market data, regulatory agency inspection reporting systems, public health information management or other existing public sector reporting systems be adapted to help track indicators to assess "expected population coverage" and trends in impact of folic acid fortification program to complement other data for decision making?
10. How can existing data sets and data collection systems (DHS, MICS, nutrition surveys, vulnerability assessments) be used or modified to ascertain risk of micronutrient deficiency and dietary gaps to better enable decision tree thinking on the mix of folic acid fortification and other nutrition programs to pursue, and with what cost-effectiveness?

Research and Knowledge Gaps: Economics of Prevention

1. We need better data on the costs of introducing mandatory fortification: for countries already fortifying with some micronutrients but not folic acid; and for countries where there is little or no mandatory fortification.
2. We need research on how to incentivize compliance with fortification regulations where these regulations are already in place

Annex F: Interviews/Videos With Hyperlinks

Additional information on the technical consultation can be viewed at: <http://micronutrientforum.org/folate-consultation/> and by viewing the video clips noted below.

VIDEO CONVERSATIONS

[Lynn Bailey \(University of Georgia\) and Lorenzo Botto \(University of Utah\)](#)

Join the Chair and Co-chair of the consultation as they discuss the progress to-date on the unique and exciting contributions the technical consultation is bringing to the fields of nutrition and birth defects.

[Homero Martinez \(Micronutrient Forum Secretariat\) and Aliko Weakland \(Core Engagement\)](#)

The Micronutrient Forum, with support from the Bill & Melinda Gates Foundation, is spearheading the Technical Consultation on Folate status in Women and NTD Prevention. Tune in to hear about this exciting work and how this work will help to advance and accelerate prevention opportunities in low- and middle-income countries.

[Patrick Stover \(Cornell University\) and Anne Molloy \(Trinity College – Dublin\)](#)

Patrick Stover and Anne Molloy discuss the science behind folic acid and NTD prevention and share how the technical consultation considered both the safety of folic acid fortification and Vitamin B12 in NTD prevention.

[Greg Garrett \(GAIN\) and John Hoddinott \(Cornell University\)](#)

Fortification of cereal grains with folic acid is an effective prevention opportunity, but we may need to explore innovative approaches to reach women of reproductive age in low- and middle-income countries. Greg and John share how the consultation is bringing prevention technologies and economics together to make the investment case for global NTD prevention.

[Robert Black \(Johns Hopkins\) and Lorenzo Botto \(University of Utah\)](#)

Understanding and obtaining the data on the burden of NTD is a difficult but necessary element for directing and advancing prevention efforts. Bob and Lorenzo talk about the challenges the global community has faced in capturing these data and how to change the landscape from what we don't know, to what we do.

Committee of the Technical Consultation: Folate Status in Women and Neural Tube Defect Prevention



Front Row (*left to right*) Anne Molloy, Homero Martinez, Lynn Bailey, Lorenzo Botto, Luz Maria De-Regil, Ken Brown.

Back Row (*left to right*) John Hoddinott, Christine Pfeiffer, Patrick Stover, Greg Garrett, Alik P. Weakland, Bob Black.

Missing: Neena Raina, Brian Anderson

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